



Data requirements and methods to support the evaluation of new vector control products

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RECOMMENDATIONS

BACKGROUND

WHO's process for the evaluation of vector control tools, technologies and approaches has been revised to better meet the needs of countries endemic for, or at risk of, vector-borne diseases. Under the revised process, the evaluation pathway to be followed is determined by whether or not a product is part of a product class with an existing WHO policy recommendation for its use.¹

Products covered by an existing WHO policy recommendation will follow the *Prequalification Pathway*, while all new tools, technologies and approaches will follow the *New Intervention Pathway*, supported by the Vector Control Advisory Group (VCAG). VCAG will validate whether the intervention under assessment has public health value.² Once public health value has been demonstrated, WHO will issue a policy recommendation.

Following a request from the Malaria Policy Advisory Committee (MPAC) in March 2017, WHO is reviewing the data requirement associated with the evaluation of new vector control interventions to ensure that these can be deployed as soon as possible, while also ensuring that policy recommendations to guide deployment remain evidence-based.

With the move to a revised evaluation system and the arrival of new vector control products, WHO must also guide assessment of products that clearly fall within an established intervention class, but that differ in product specification and/or design (e.g. location of insecticide or synergists on panels of mosquito nets) from the first-in-class product that established the class and for which epidemiological data are available. For such new products, WHO requires reassurance of similar performance (for disease or vector control) to provide normative guidance to vector control programmes faced with the challenge of selecting a reliable product. Examples of such

products included mosquito nets treated with a pyrethroid and the synergist piperonyl butoxide (PBO), new indoor residual spray (IRS) chemistries, and new mosquito larvicides and space spray products.

To discuss these areas in detail so as to provide recommendations to MPAC and WHO, an evidence review group (ERG) was jointly convened by the WHO's Global Malaria Programme, the Department of Control of Neglected Tropical Diseases, and the Prequalification Team for Vector Control Products from 12–14 September 2017.³ The ERG was tasked with reviewing summarized laboratory and field trial data for selected new vector control products and to use these as case-studies to develop both product specific policy recommendations and general recommendations in support of the evaluation process for new vector control tools, technologies and approaches.

CONCLUSIONS AND RECOMMENDATIONS

On the basis of the current evidence, the ERG advises WHO as follows:

Specific conclusions and recommendations on SumiShield® 50WG

Conclusions and recommendations in this section are based on a review of summarized results from a laboratory study (IRD, France) and experimental hut⁴ and long-term large-scale⁵ community trials from Tanzania, India, Côte d'Ivoire and Benin. These trials measured entomological endpoints only.

1. **SumiShield® 50WG meets the current WHO efficacy criteria for IRS.**⁶
This conclusion is based on the review of mortality data for fully insecticide susceptible *Anopheles* mosquitoes exposed in cone-bioassays to walls treated with a target dose of 300 mg AI/m². Percentage mortality 24 hours after 30-minute exposure was equal to or greater than 80% for most studies and exceeded this threshold after a 72-hour holding period in all studies for a duration of 4–8 months following application of the insecticide to walls. If the trial results had been assessed by a former WHOPES Working Group, SumiShield® 50WG would have met the efficacy criteria and been recommended for use as an IRS product.
2. **SumiShield® 50WG has a similar entomological effect to other IRS products that are currently covered by a WHO policy recommendation.**
A similar entomological effect is here defined in terms of the speed with which SumiShield® 50WG kills mosquitoes over defined holding/recovery time periods (24–72h) after a standard exposure time (30 minutes) and as measured by means of post-exposure percentage mortality with cut-off of ≥80%. Based on data from the studies in Tanzania, which explicitly compared SumiShield® 50WG (target dose: 300 mg AI/m²) to the pyrethroid deltamethrin (K-Othrine 250 WDG; target dose 25 mg AI/m²), the organophosphate pirimiphos methyl (Actellic 300 CS; target dose 1g AI/m²) and the carbamate bendiocarb (Ficam 80WP; target dose: 400 mg AI/m²), SumiShield® 50WG was found to perform as well as, or better than, these comparator products. The evidence presented also indicated improved performance for extended holding times post exposure in cone bioassays (i.e. higher mortality after 72 hours when compared to 24 hours and adjusting for mortality in controls). A similar effect was seen for the positive control products.

3. **Existing WHO policy recommendations for IRS should be extended to include SumiShield® 50WG.** While the insecticide belongs to a different chemical class – the neonicotinoid insecticides – its similar entomological effect to that of other IRS products currently covered by WHO policy supports the extension of this policy to SumiShield® 50WG. Any other neonicotinoid insecticide submitted for evaluation to WHO will also be required to demonstrate that it meets the minimum efficacy criteria for IRS to be covered under current policy.
4. **National malaria control programmes and their implementing partners should consider deployment of SumiShield® 50WG for IRS.** Deployment must only be considered in situations where coverage with effective vector control (primarily long-lasting insecticidal nets (LLINs) or IRS) will not be reduced; the primary goal must remain the achievement and maintenance of universal coverage for all people at risk of malaria.
5. **Data generation to document the epidemiological impact achieved through deployment of SumiShield® 50WG is strongly encouraged.** The extension of WHO policy to the neonicotinoid insecticide SumiShield® 50WG is based only on entomological data, and an assumption that a similar or better entomological effect observed when compared to other IRS products covered by WHO policy will translate into at least a similar epidemiological impact. This assumption requires confirmation following deployment of SumiShield® 50WG in control programmes.

GENERAL RECOMMENDATIONS

1. **New IRS, space spray and larvicide products should be considered as covered by the WHO policy for those product classes if they (1) have the same entomological effect as products in the classes covered by WHO policy and (2) meet the WHO efficacy testing criteria for the relevant product class, even if their biochemical mode of action differs.** The key criteria to be met are based on current WHO testing guidelines^{6,7} and are as follows:
 - IRS products will need to demonstrate insecticidal action against susceptible anopheline mosquitoes above the efficacy cut-off point in WHO cone bioassays. Accordingly, the duration during which mosquito mortality is $\geq 80\%$ after 30 minutes exposure on the treated substrate and a 24-hour holding period is recorded. Knockdown after 60 minutes post-exposure is also recorded, but there is no WHO cut-off for this parameter. Other entomological parameters are also investigated in experimental hut studies to demonstrate the behavioural and insecticidal action of the candidate insecticide products.
 - For space spray products the minimum dosage needs to be determined that gives at least 90% mortality after 60 minutes of exposure and 24 hours holding against laboratory reared non-blood fed susceptible strains held in confined screen cages in the field.
 - For larvicides the minimum dosage needs to be determined that achieves 80% or 90% mortality, or adult emergence inhibition (the desired level of control).

The ERG recommends that revision of current testing guidelines, as outlined under general recommendation 5, includes a review of current testing criteria with a view of enhancing their clarity.

2. **New IRS, space spray and larvicide products that do not meet the current WHO testing criteria, and hence differ in their entomological effect from products covered by WHO policy, need to be assessed by VCAG to determine their public health value.** Part of this evaluation process consists of the establishment of testing criteria for the new product and for the new intervention class that this “first-in-class” product creates. The requirement will be to demonstrate public health value.² A claim of efficacy against resistant mosquitoes or any other specific claim will need to be demonstrated as part of the evaluation. It is recognized that demonstration of claims, such as efficacy against insecticide-resistant mosquitoes, may require additional guidance from WHO and revision of the existing WHO test procedures (see general recommendation 5) and thresholds. For novel product classes (and to stimulate innovation) manufacturers should not feel tied to test procedures or threshold criteria established for existing classes during their development of new product classes.
3. **New LLIN products that are not covered by an existing WHO policy need to be assessed by VCAG to determine their public health value.** This requirement is based on the complexity of how LLINs provide personal and community-level protection, whereby entomological outcomes are currently not considered to be reliable indicators of epidemiological impact, especially in areas of pyrethroid resistance.⁸ As part of the evaluation process, testing criteria will need to be established for the new product and for the new LLIN intervention class that this “first-in-class” product creates.
4. **New vector control products that have the same biochemical mode of action and entomological effect as a product in a class covered by WHO policy should be required to:**
 - Meet current testing criteria for the product class based on laboratory and small-scale field trials⁴ and large-scale field trials⁵ with entomological endpoints. Current guidance for each intervention type (LLINs, IRS, larvicide, etc.) should be consulted and will need to be updated to include details on determination of non-inferiority (see below).
 - Demonstrate non-inferiority⁹ to at least one existing product in the product class by means of small-scale field trials (i.e. experimental hut studies in the case of LLINs and IRS products).
 - For pyrethroid-PBO nets, a set of criteria will need to be defined for PBO persistence over time, including not only that PBO is retained in the net but is also replenished and bio-available as a synergist on the surface of the netting fibres.

If a manufacturer wishes to expand the claim of a product covered by WHO policy, for example to include efficacy against insecticide resistant vectors, data to substantiate this claim will need to be reviewed by WHO.

5. **To support the general recommendations made under points 1–4, WHO is requested to conduct further work in a number of key areas with the aim of refining or modifying current evaluation guidance and procedures:**
 - Assessment of non-inferiority of products within a class. While entomological field studies, in particular experimental huts, may provide a suitable approach for the determination of non-inferiority, the design of such trials needs to be reviewed and additional guidance developed to support implementation of a standardized and rigorous study design and analysis. An in-depth assessment of existing experimental trial

data from different settings and a comparison of statistical methods to analyse new and existing experimental trial data are required. Based on these analyses, specific guidance on assessment of non-inferiority should be developed and incorporated into a revision of current WHO testing guidelines.

- The design, execution and reporting of entomological field trials need to be reviewed and additional guidance developed to support implementation of high quality studies and standardized reporting to facilitate assessment of data by WHO advisory groups. Revised guidance should include details on randomization, replication and power calculations.
- Investigation of the relationship between entomological outcomes, generated through laboratory and small-scale field trials,⁴ and epidemiological and vector-transmission outcomes (e.g. reductions in entomological inoculation rate and vector density), generated through cluster randomized trials (CRTs), should be explored to determine whether entomological markers of intervention effects can be identified that are reliable surrogates for effects on disease endpoints. At present, there is a paucity of evidence to assess whether entomological effects determined in laboratory or small-scale field trials⁴ predict epidemiological outcomes determined in CRTs. This is, at least partially, due to the limited amount of data from CRTs available to explore such relationships, as few CRTs were conducted to assess vector control interventions in recent years. It is recommended that experimental hut trials (in the case of IRS, LLIN and other indoor acting products) be carried out, if possible, in the vicinity of the CRT to establish or improve knowledge of the relationship if there is spatial heterogeneity in local species or its resistance profile. It is also recommended that investigation of potential surrogate markers and critical efficacy thresholds should focus on sampling the products during CRT evaluation and test in laboratory bioassay, experimental huts or semi-field system. Investigation of potential surrogate markers should focus initially on products that have demonstrated public health value in CRTs or are undergoing CRT evaluation. These should be tested in a variety of entomological laboratory and small-scale field trials⁴ to identify which, if any, testing methods generate data that provide reliable entomological surrogates for effects on disease endpoints.
- For space sprays, the current test methods should be reviewed to ensure that products also demonstrate efficacy against wild mosquitoes in large-scale field trials.⁵ Additional guidance and criteria will need to be developed, including the requirement for cage controls of field derived target species mosquitoes and for droplet counts to ensure that products are applied according to target dosage or manufacturers requirements.
- To better allow assessment of product efficacy in the field in the presence of resistance, WHO should update testing guidance to include testing in laboratory studies against resistant mosquito strains, including all major resistance mechanisms. In addition, in field studies, product efficacy against local mosquito populations representative of prevailing patterns of resistance should be assessed.
- For IRS products, the ERG recommends that, in case where convincing evidence is presented for $\geq 80\%$ mortality following a 72-hour holding period this criteria should be considered in the assessment of the product; revision of testing guidelines should include this criteria. For all new IRS products, data from 30-minute exposure in cone bioassays with both 24-hour and 72-hour holding periods should be presented to

allow assessment of delayed mortality. The ERG also recommends that a minimum threshold for the duration of insecticidal efficacy of three months, after application of the insecticide to the walls, be included as a criteria for minimum efficacy.

- Discussion around deployment guidance was not within the scope of this ERG, and should be discussed by another WHO advisory group, particularly to address utility of products for insecticide-resistance management.

6. **Generation of high quality evidence beyond that generated through existing evaluation methods is encouraged to facilitate product evaluation and the formulation of policy and programmatic guidance.**

Specific areas in which WHO is requested to conduct further work are listed below:

- The WHO Department of Control of Neglected Tropical Diseases and the Global Malaria Programme are requested to conduct a review of the policies for the evaluation of space sprays and larvicides/larvicidal devices to guide the generation of the required additional evidence to determine their public health value and hence provide an evidence-base to support continued use of these products, technologies or approaches. Larviciding with chemicals is used widely to treat *Aedes aegypti* larval habitats, and should be considered as complementary to environmental management and should be restricted to containers or fixed habitats that cannot otherwise be eliminated or managed. Overall, there is a paucity of evidence of effects on disease endpoints for vector control measures such as space spraying and larvicides/larvicidal devices. Such evidence should be generated and systematically reviewed to support the use of these interventions for public health purposes. Space spraying is currently recommended for control only in emergency situations to suppress an ongoing dengue/arboviral disease epidemic or to prevent an incipient one. The objective of space spraying is the massive, rapid destruction of the adult vector population. Any control method that reduces the number of infective adult mosquitoes, even for a short time, should reduce virus transmission during that time, but it remains unclear whether the transient impact of space treatments is epidemiologically significant. Factors such as insecticide susceptibility, droplet size, application rate, frequency and indoor penetration of the insecticide are all crucial to the efficacy of application of this method for controlling *Ae. aegypti*. A recent review concludes that indoor space spraying is an effective adulticidal intervention against *Aedes* mosquitoes.¹⁰ However, WHO needs to periodically review and build a stronger evidence base for the impact of indoor space spraying on the disease.
- Multiple comparisons of products of different chemical classes in experimental hut studies⁴ are encouraged to identify the appropriate comparator product for large-scale field trials.⁵ Such data are also helpful to inform rotation of active ingredients for resistance management.

7. **In view of the existing threat caused by insecticide resistance, the development and evaluation of products that are explicitly designed to control insecticide-resistant mosquitoes is encouraged.** These products should come with a claim of being effective in settings where the vectors are resistant to one or more insecticide classes and should be evaluated against this claim.

Endnotes

1. The evaluation process for vector control products. Geneva: World Health Organization ; 2017 (<http://www.who.int/malaria/publications/atoz/evaluation-process-vector-control-products/en/>)
2. A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans.
3. The present document reflects the content of a document presented to MPAC under the title *Data requirements and methods to inform the potential extension of WHO policy to new vector control products and to verify the performance of products entering an established class* by the ERG on Assessing Comparative Effectiveness of New Vector Control Tools (<http://who.int/entity/malaria/mpac/mpac-oct2017-erg-comparative-effectiveness-report-session5.pdf>).
4. Formerly referred to as WHOPES Phase II evaluation
5. Formerly referred to as WHOPES Phase III evaluation
6. Guidelines for testing mosquito adulticides for indoor residual spraying and treatment of mosquito nets. Geneva: World Health Organization; 2006 (http://apps.who.int/iris/bitstream/10665/69296/1/WHO_CDS_NTD_WHOPES_GCDPP_2006.3_eng.pdf)
7. Guidelines for laboratory and field testing of mosquito larvicides. Geneva : World Health Organization ; 2005. (http://apps.who.int/iris/bitstream/10665/69101/1/WHO_CDS_WHOPES_GCDPP_2005.13.pdf)
8. Malaria vector control policy recommendations and their applicability to product evaluation. Geneva : World Health Organization; 2017 (<http://www.who.int/malaria/publications/atoz/vector-control-recommendations/en/>)
9. A vector product under evaluation shows non-inferiority when it demonstrates an equal or better entomological effect and/or protective efficacy against infection and/or disease in humans than the comparator product. Non-inferiority relies on a measurement of effect whereby the difference should be only a small amount, called delta. Delta is pre-specified based on the desired clinical (or entomological) effect. Specifying a smaller delta for a non-inferiority trial can test whether a new product's performance is similar to that of a comparator product (i.e., effect is $<\delta$), but demonstrating statistical significance may require larger sample sizes.
10. Maoz et al. (2017) Community effectiveness of indoor spraying as a dengue vector control method: A systematic review. PLoS Negl Trop Dis. 2017 Aug 31;11(8):e0005837